

Simple adaptive mobile phone screen illumination for dual phone differential phase contrast (DPDPC) microscopy

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Abstract: Phase contrast imaging is widely employed in the physical, biological, and medical sciences. However, typical implementations involve complex imaging systems that amount to in-line interferometers. We adapt differential phase contrast (DPC) to a dual-phone illumination-imaging system to obtain phase contrast images on a portable mobile phone platform. In this dual phone differential phase contrast (dpDPC) microscope, semicircles are projected sequentially on the display of one phone, and images are captured using a low-cost, short focal length lens attached to the second phone. By numerically combining images obtained using these semicircle patterns, high quality DPC images with ≈ 2 micrometer resolution can be easily acquired with no specialized hardware, circuitry, or instrument control programs.

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1. Introduction

In bright-field microscopy, when imaging pigmented or amplitude samples, the contrast in the resulting images is created due to greater light absorption in the denser regions of the sample, leading to absorption-based optical contrast. However, most biological specimens lack intrinsic absorption contrast and require exogenous staining for visualization. When imaging these transparent samples, light will simply pass through without any amplitude attenuation, which creates little to no contrast in the resulting images, making the sample difficult to observe. As staining is complex to perform in general, several optical methods have been developed to allow visualization of unstained, transparent samples, such as dark-field microscopy, polarized microscopy, and, most commonly, phase contrast (PC) microscopy.

First reported by Frits Zernike in the beginning of the 1930s [1], for which he was awarded the Nobel Prize in 1953, PC microscopy helped drastically improve biological imaging of unstained cells and thin tissue slices. PC microscopy works by interfering light paths that have not interacted with the specimen with those that have. Due to refractive index differences between the sample and the surrounding medium, phase shifts accrued by light passing through the sample are transformed into intensity differences due to this interference process, thus generating optical contrast. While classical PC microscopy requires the addition of annular illumination and conjugate phase rings in the back aperture of the objective, differential interference contrast microscopy [2,3] requires the use of polarizers and prisms to be able to further highlight small differences in the refractive index within different parts of the sample. Additional exotic configurations exist, such as Hoffman modulation contrast microscopy [4], which uses oblique illumination to amplify contrast in the sample by employing an off-axis slit aperture as well as an optical amplitude spatial filter.

The above-mentioned techniques improve contrast, leading to a qualitative enhancement of the image. Yet, the phase information in the image is purely qualitative, because the interference as

measured in these cases lacks a stable reference. However, the ability to obtain quantitative phase information could provide more meaningful criteria for image comparison, as well as useful information about the sample, such as sample height, or dry mass [5]. These potential benefits led to the development of quantitative phase contrast microscopy, or Quantitative Phase Imaging (QPI) [6–9], which not only provides contrast, but also produces phase images, which depict the actual values of the phase shift variations at each pixel in the image. This, in turn, allows the user to extract refractive index values and spatial dimensions of the objects in the image, or to re-cast the data with controllable contrast *a posteriori* [10].

In the last decade or so, several groups have developed QPI methods, and demonstrated their application to practical problems, including cell-level drug resistance [11], cancer diagnostics and dynamics [12–14], red blood cell imaging and characterization [15–17], malaria diagnosis [18,19], among many others. Several groups have extended QPI to compact measurement systems, such as mobile phone-based microscopes [20–22], or lab-on-chip devices [23]. While these systems have shown excellent utility, the optical setup for these techniques can be rather complex, bulky, and expensive, generally requiring careful alignment of the optical components, and exotic components such as spatial light modulators. Consequently, there has been increasing interest in simplifying these systems by combining controllable illumination with computational methods to reconstruct quantitative phase images without the need for a stable phase reference or phase shifting interferometry. In particular, recent studies have focused on using spatially variable illumination sources in QPI, such as LED arrays [24] or traditional microscope illuminators coupled to spatially addressable pixelated liquid crystal displays (LCDs) [25]. Using a controllable illumination system and acquiring several images in sequence, with the illumination changing between each image, allows for the computational reconstruction of qualitative [26] and quantitative phase images [27]. Further work has shown that in addition to QPI images, one can use this programmable illumination to recover 3D imaging volumes [28], perform Fourier ptychographic microscopy [29], and correct aberrations within the imaging system. As the illumination system is relatively low cost, such an approach naturally lends itself to small and portable imaging systems, including those built on single-board computing platforms such as mobile phones [30,31] that can further include deep learning algorithms [32].

However, while the optical configuration in these systems can be quite simple, and thus vastly improve on traditional phase microscopes and QPI systems, a key drawback of the adoption of such methods by non-experts is the complex electronics needed to create and control these spatially variable illumination sources. Previously, we showed that a mobile phone-based microscope [33] could be placed to face a mobile phone screen, where the screen of the second phone is used as a controllable illumination source [34]. Such a dual-phone illumination-imaging microscope could easily mimic traditional microscope modalities such as bright-field, dark-field, and fluorescence, by controlling the color and spatial distribution of the illumination. It also showed the ability to easily obtain quite complex illumination schemes such as Rheinberg illumination. Critically, the illumination source does not require specialized computer control, a microcontroller, or any associated electronics. A user simply draws the desired illumination pattern as an image, or as a “slide” in Microsoft PowerPoint or a similar presentation program, and the phone natively displays the correct illumination. Switching between illumination schemes is as simple as swiping a finger on the display. Thus, our dual-phone illumination-imaging system is extremely amenable to use by non-experts in field settings.

In this paper, we extend our prior work to phase contrast imaging, where we use one mobile phone for imaging, and another for illumination to generate semi-circular illumination patterns that can be used to compute differential phase contrast (DPC) images. Compared with prior systems [30,31], our dual phone DPC (dpDPC) system is not only more compact and portable, but the use of a phone screen with densely packed RGB LEDs for illumination instead of an LED array or LCD allows for complex spatial patterns, intensity gradation, and color generation, as

well as more pattern options to be explored. These benefits are all obtained without requiring specialized control software or utilizing complex electrical wiring. As detailed below, our system obtains good quality phase contrast images, with resolutions below 2 micrometers, of a wide variety of samples, including polystyrene beads, blood smears, and cell cultures.

2. Results and discussion

2.1. Description of the imaging and illumination platforms

To build an illumination-imaging platform capable of differential phase contrast (DPC), we adapted the dual-phone illumination-imaging system described in [34], and the asymmetrical illumination DPC generation concept described in [24] to produce images that can be later combined to generate DPC images. To demonstrate the generalizability of the illumination scheme, we performed imaging using a mobile phone microscope as shown in Fig. 1(a), as well as using a low-cost traditional microscope with on-board camera module (Fig. 1(b)). In both cases the illumination platform consists of the display of a mobile phone.

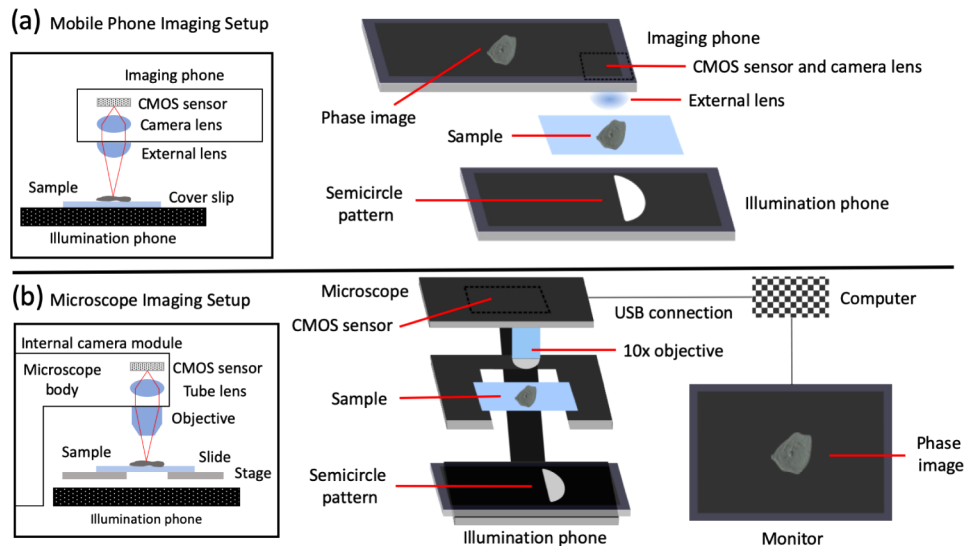


Fig. 1. Description of the systems and components. (a) Sketch of the overall optical (left) and physical (right) setup of the mobile phone-based imaging system and the illumination system. (b) Sketch of the overall optical (left) and physical (right) setup of the low-cost traditional microscope imaging system and the illumination system.

Figure 1(a) shows the optical setup of the mobile phone-based imaging system and the illumination system (left), as well the physical setup (right). The imaging system in this case consists of a Nokia mobile phone, with an attached external lens (iPhone 5 lens: $NA = 0.23$, $f2.2$), that provides a 2x optical magnification, while the illumination system is a Retina display of an Apple iPhone 6. As shown in the figure, we projected semicircle patterns on the screen of the illumination phone to create asymmetrical illumination and produce the differential phase contrast images as described in Section 2.2. The sample was then mounted on top of the illumination screen (at a distance of 25 cm), and images were collected by the imaging phone. These images can then be displayed directly through the phone camera software, or transferred to a computer for further analysis using ImageJ.

Figure 1(b) shows the optical setup of the microscope-based imaging system and the illumination system (left), as well the physical setup (right). The imaging system in this case consists of a

microscope with an on-board camera module, utilizing a 10x, 0.25 NA objective. Once again, we projected semicircle patterns on the screen of the illumination phone (in this case a Xiaomi Redmi 3S), the sample was mounted on the sample stage, at a distance of ≈ 20 mm from the illumination screen, and the imaging was performed by the camera module. The camera module is connected to the computer via USB. Image analysis is then performed identically to the dual-phone setup.

2.2. Generation of differential phase contrast (DPC) images

Images taken with semicircle illumination patterns display phase information of the sample, with each semicircle orientation resulting in phase images along a specific axis. In order to acquire the differential phase contrast information along a single axis, a normalized difference of images taken with semicircle patterns of opposite orientations is performed, as shown in Eq. (1), to produce the final dpDPC image [27,35].

$$I_{DPC} = \frac{I_1 - I_2}{I_1 + I_2} \quad (1)$$

where I_1 and I_2 represent either left and right or top and bottom images obtained with semicircle illumination. Example calculations are shown in Fig. 2, where images of human epithelial cheek cells (HECCs) taken with semicircle patterns with top-bottom, and left-right orientations, are combined to produce the final dpDPC image. The normalized difference of images taken with top-bottom semicircle orientations results in a DPC image with highest resolution along

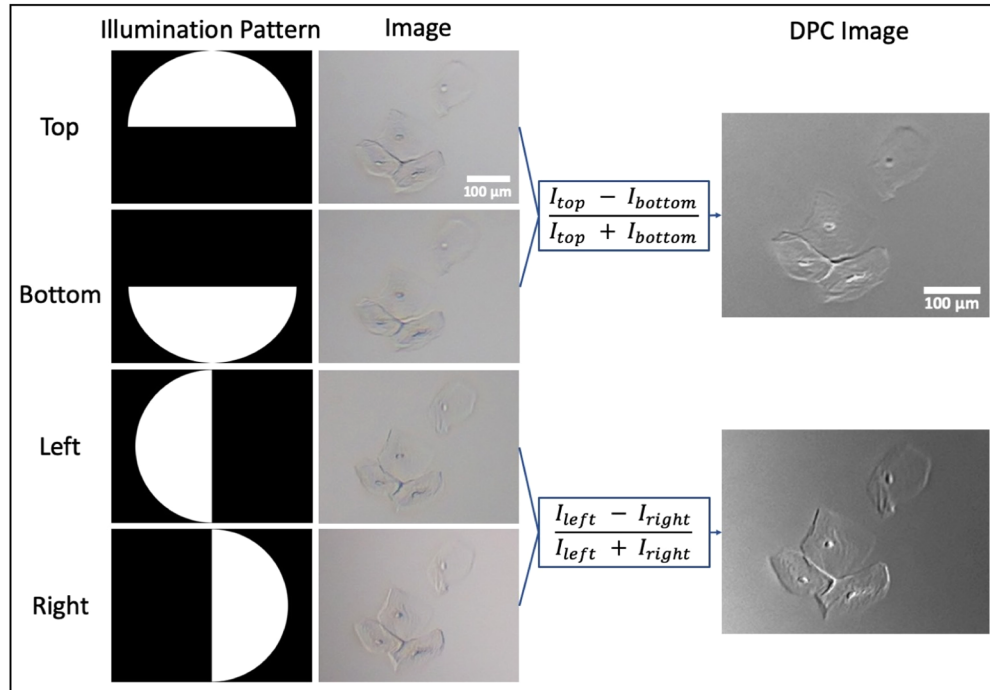


Fig. 2. Image computation for production of dual-phone differential phase contrast (dpDPC) images. Successive images of human epithelial cheek cells (HECC) using top-, bottom-, left-, and right-semicircle illumination patterns: I_{top} , I_{bottom} , I_{left} , and I_{right} , respectively. The final DPC image shown on the top-right is obtained by using the normalized difference of I_{top} and I_{bottom} along the vertical axis. The final DPC image shown on the bottom-right is obtained by using the normalized difference of I_{left} and I_{right} along the horizontal axis.

the vertical axis, and performing the same steps with images taken with left-right semicircle orientations results in a DPC image with highest resolution along the horizontal axis. These can be combined into a 4-axis DPC image with laterally isotropic resolution as described in [24], yet with the caveat that the reconstruction is no longer mathematically trivial, and is therefore not as amenable to non-experts.

For this to work, system alignment needs to be performed, as alignment issues can significantly alter the appearance of images. Misalignment can be caused by either the imaging system (external lens and phone camera) or by the illumination system. Typically, the external lens is hard mounted onto the phone and great care is taken that it is well aligned with the optical axis of the phone detector and camera-lens system. On the other hand, the illumination circle needs to be aligned with the optical axis of the imaging system in order to obtain high quality contrast images. This is performed by centering the illumination circle within the field of view (on the screen) of the imaging phone. Then, by maintaining this alignment, half circles of the original circle are produced, and images are collected as described earlier. When the circle is not well aligned with the optical axis of the imaging phone, the intensity gradient of the illumination for left-illumination and right-illumination images is different, which will lead to a composite DPC image that exhibits a high degree of nonuniform illumination with poor quality of phase reconstruction.

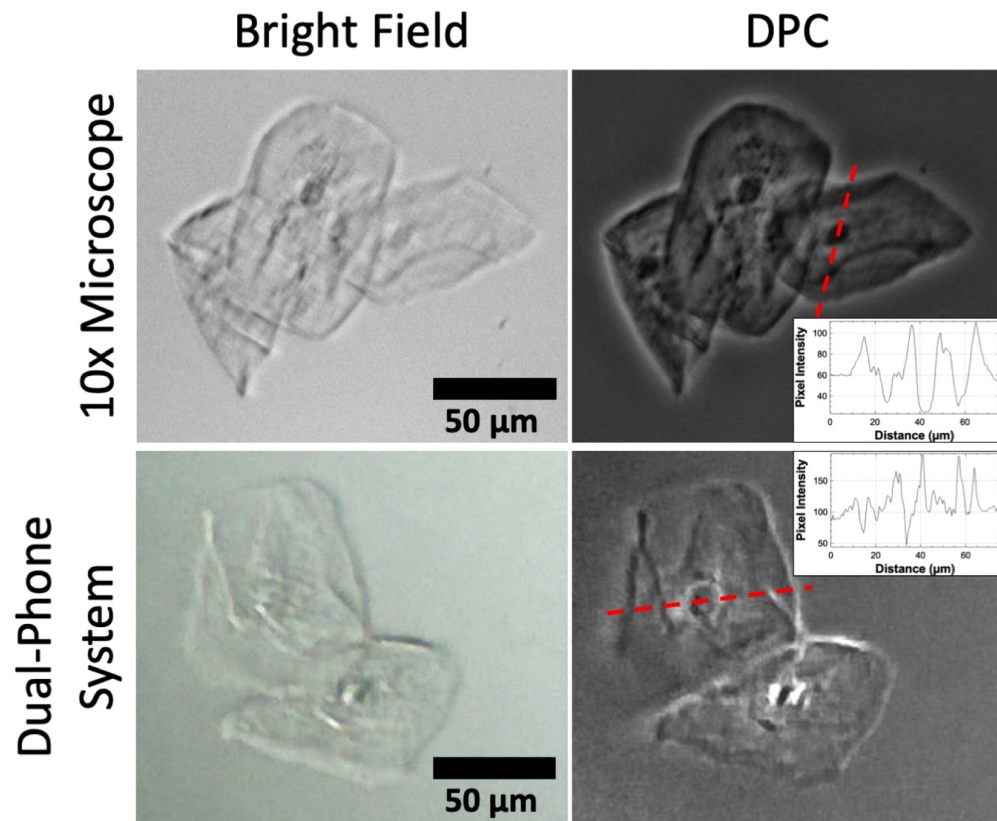


Fig. 3. Comparison of DPC images. BF (top-left) and PC (top-right) images of HECC taken with a traditional microscope, using a 10x phase contrast objective with $NA = 0.25$. BF (bottom-left) and dpDPC (bottom-right) images of HECC taken using the dual-phone illumination-imaging system described in this paper. The insets on the right show pixel intensity plots generated across individual cells for both DPC images.

The resulting DPC images were also compared with phase contrast images taken with a custom-made microscope that employs traditional phase contrast microscopy (10x, 0.25 NA objective), as shown in Fig. 3. The images show comparable phase contrast image quality using a much simpler setup. Changes in pixel intensity across individual cells were also plotted for both DPC images, and are shown as insets within the figure. As can be seen in the plots, a large number of fine intensity fluctuations can be observed across the cells that had been imaged using both the microscope and the dual-phone system, which corresponds to features present in the image.

2.3. *Application of the mobile phone-based imaging system to DPC microscopy of cells*

Figure 4 shows both BF and dpDPC images of polystyrene beads, which are typically imaged for system calibration purposes (such as for determining resolution and image warping), mouse monocyte macrophage cells (J774A.1 cells), and mouse embryonic carcinoma cells (P19 cells). More specifically, we demonstrate the quantitative capabilities of the dual-phone system in terms of contrast and performing accurate cell measurements. First, an improvement in contrast of the dpDPC compared with BF is observed for all samples, as follows: (i) for beads, 0.22 contrast for BF, and 0.26 contrast for dpDPC; (ii) for monocytes, 0.11 contrast for BF, and 0.27 contrast for dpDPC; (iii) and for P19 cells, 0.09 contrast for BF, and 0.26 contrast for dpDPC. In addition, morphological parameters such as diameter, length measurements, and area are provided as well.

In Fig. 5, we show dpDPC images of mouse neuroblastoma cells (N2a cells), and both live and dead mouse bone marrow-derived macrophages. These images provide a qualitative evaluation of the capabilities of the system, demonstrating that it can be used to image numerous samples of practical relevance, differentiate various cell types, and assess cell viability. Generally, bright-field (BF) images of such cells exhibit poor contrast, and consequently the overall cell structure is poorly defined. Moreover, obvious subcellular organelles, like the nucleus, as well as density variations along the cell area, are difficult to visualize. However, dpDPC images provide reasonable image quality over a wide field-of-view, with some ability to resolve subcellular detail. The enhanced contrast afforded by PC microscopy as shown in Figs. 4 and 5 could be utilized in future studies for identifying water-borne parasites [37], or simple monitoring of cell culture growth or confluence.

2.4. *Application of the phone illumination to DPC microscopy of cells using a low-cost microscope*

To demonstrate the adaptability and versatility of this illumination-imaging system, we tested the same illumination setup with a different imaging platform, namely a traditional microscope imaging system. By placing the phone underneath the sample in a low cost, upright microscope, we acquired images of HECC (top) and a Wright-Giemsa-stained blood smear (bottom) (Fig. 6). In this figure we show a comparison between BF and DPC images obtained with this setup.

As expected, due to the higher quality optics, the image quality using a traditional, low-cost microscope is slightly higher than that of the mobile phone system. However, the improved image quality comes at the cost of portability and the need for a separate computer. In this optical system, that does not have phase-contrast capability, by simply removing the condenser lens from the system and placing the phone on top of the condenser support structure, DPC images can easily be obtained. To further demonstrate the versatility of the system, the Retina display screen of the iPhone was replaced in these experiments by that of a lower-cost Xiaomi Redmi 3 phone, with essentially identical results.

A comparison between BF and DPC images very clearly shows the marked improvement in contrast that can be achieved using a very simple and flexible illumination source, even on samples with their own absorption contrast, such as the stained blood smear. In this particular

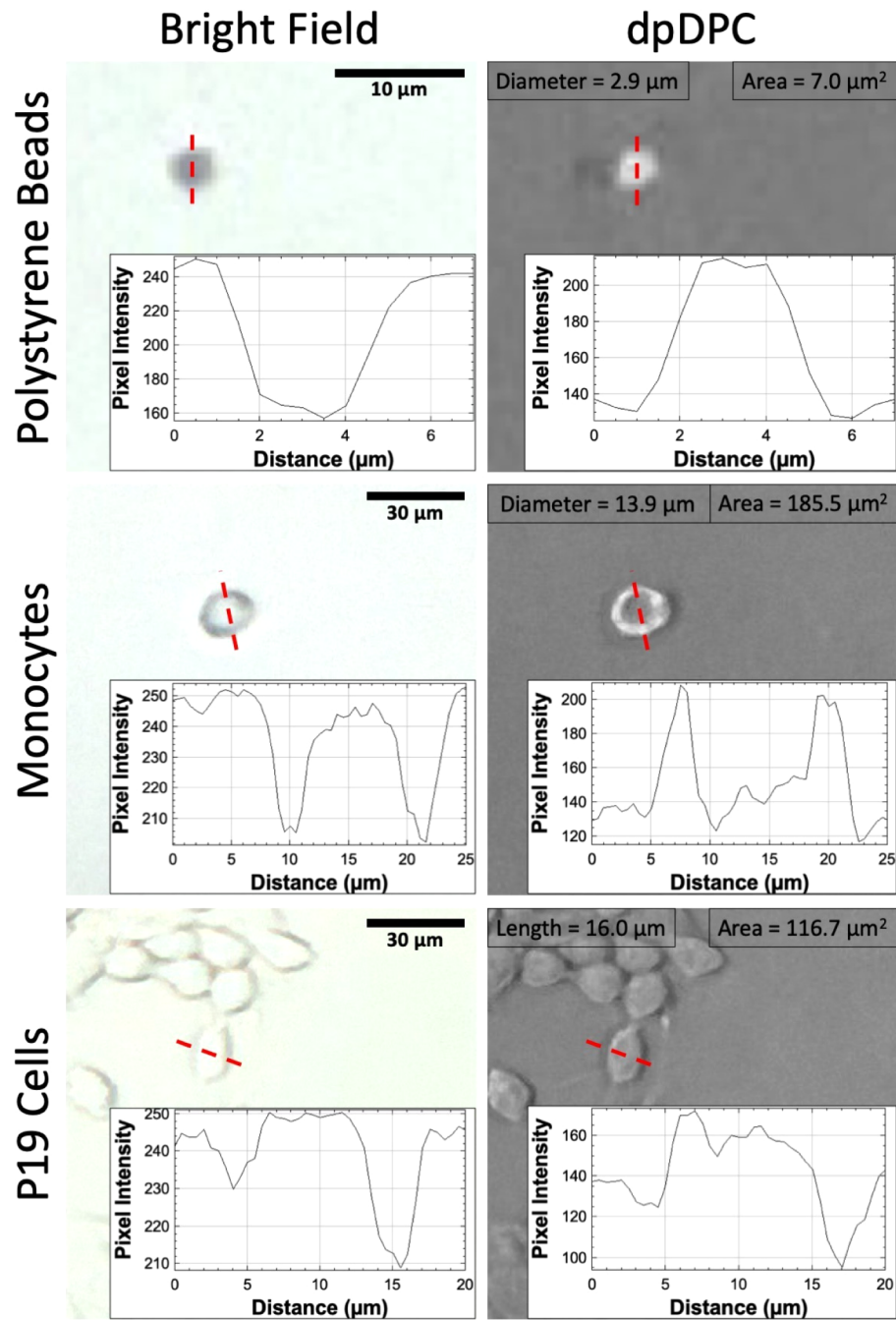


Fig. 4. Application of dpDPC microscopy to quantitative cell imaging. Bright-field and dpDPC images of 3 μm polystyrene beads, monocytes, and P19 cells. The respective insets show the pixel intensity profile across a single cell. dpDPC images also show cell dimension and area measurements.

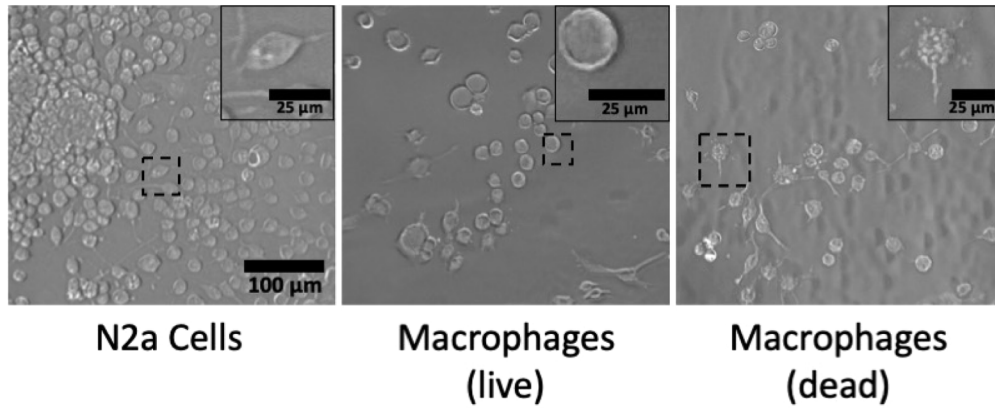


Fig. 5. Application of dpDPC microscopy to qualitative cell imaging. dpDPC images of N2a cells, and both live and dead macrophage cells, with each respective inset showing a magnified image of an individual cell of that cell type.

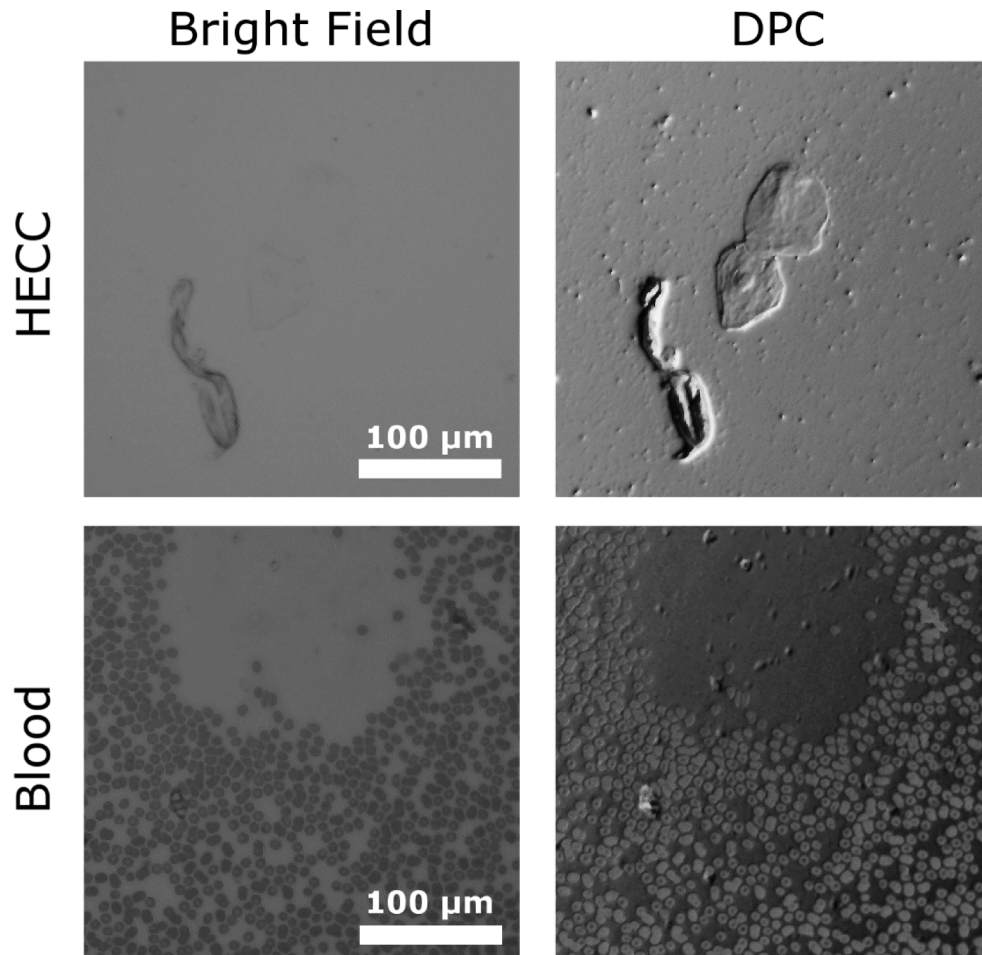


Fig. 6. Application of phone illumination to DPC microscopy of cells using a low-cost microscope. BF and DPC images of HECC (top) and a WG-stained blood smear taken with a low-cost microscope that does not have PC capability, where the illumination has been replaced with a mobile phone screen exhibiting semicircle patterns for DPC microscopy.

case, the DPC images are of higher quality than the BF images, which makes it easier to perform a cell count. A manual cell count of approximately 795 RBCs can be measured, highlighting the potential to provide clinically relevant information such as blood counts [33,36]. Through the use of a mobile phone, rather than a more complex electronic system, DPC images can be acquired through simple manual positioning of the mobile phone, followed by swiping through various slides in a PowerPoint presentation. Thus, this illumination geometry completely eliminates the need for any expertise in system construction or electronic control.

3. Conclusion

In this paper, we demonstrate the ability of our multi-modal dual-phone illumination-imaging microscopy system [34] to perform differential phase microscopy (dpDPC). We demonstrate dpDPC images of multiple mammalian cell types, namely human epithelial cheek cells (HECC), a blood smear, mouse monocyte macrophage cells (J774A.1 cells), mouse neuroblastoma cells (N2a cells), mouse embryonic carcinoma cells (P19 cells), and mouse bone marrow-derived macrophages, as well as polystyrene beads. Critically, the illumination, image acquisition, and system control utilize familiar phone applications such as PowerPoint and the native Camera app, and do not require any specialized knowledge in microcontroller programming, or circuit design. Thus, the system is optimized for widespread adoption by users such as medical professionals and field workers who may not be highly trained in instrument control.

We also show that this setup can be generalized beyond mobile phone microscopy by utilizing our phone illumination with a traditional microscopy platform, demonstrating that by simply placing a phone in the illumination path of a low-cost microscope without phase contrast capability, high-contrast, high quality phase images can be obtained with no special system modifications or electronics expertise.

In this paper we focus only on the qualitative DPC imaging, as the emphasis is on an imaging system and analysis method that does not require a trained operator. However, in future studies quantitative phase information could be extracted, as described in [27], from images obtained with a similar or modified system. This quantitative phase information could expand the potential application space to exploring cellular response to drugs [11], cell malignancy [14], and myriad other applications.

We finally highlight that while in this paper we describe using our dual-phone system for phase imaging, our system can at the same time acquire bright field, dark field, fluorescence, and Rheinberg illumination, all by simply changing the displayed image on the phone's screen. Further, this flexible and intuitive illumination can be extended to traditional microscopy systems where illumination geometries such as Rheinberg illumination are typically too exotic to include on low-cost general purpose microscopes commonly available in educational or even clinical settings.

This system can thus serve as a portable, adaptable low-cost microscope or microscope add-on that is capable of multi-modal imaging at a much lower cost than traditional systems, without the need for specialized phase contrast objectives or addition of further hardware that could be difficult for non-experts to control. Moreover, the setup is quite versatile in terms of its components, where other phones, platforms, or combinations of both can be used, thus adding to its accessibility. We therefore believe that such a system will find widespread use among doctors, biologists, and others who may not be experts in hardware design, to solve challenges such as low-cost monitoring of cell cultures, water quality, or blood testing, among other potential applications.

4. Experimental

4.1. Imaging

For phone-based imaging, we used a Nokia phone (Lumia 1020 model), which has a 41.3-megapixel (MP) image sensor, and a sensor pixel size of 1.12 μm . Furthermore, we attached an external lens (iPhone 5 lens: NA = 0.23, f2.2, 2x magnification) to the camera for enhanced focus. The imaging and illumination phones were clamped in place, and the sample was mounted onto an XYZ-translation stage (Thorlabs Inc.) for manipulation. The images were captured using the Lumia Camera application.

As for imaging with the low-cost microscope, we used a Jiangnan Electro-Optics DN-10B microscope (Nanjing, China), which comes equipped with a 3 MP image sensor, with a pixel size of 4.5 μm . Images were acquired with a 10x, 0.25 NA objective.

4.2. Illumination

For illumination using the dpDPC system, we used a Retina display (12 cm diagonal) of an Apple mobile phone (iPhone 6), with a pixel density of 326 pixels per inch (PPI), which is equivalent to an RGB pixel size of $\approx 78 \mu\text{m}$. Moreover, the semicircle patterns projected onto the screen were designed using the Microsoft PowerPoint application for iOS. The illumination screen was placed approximately 25 cm below the sample, and was aligned in such a way that the center-line of the DPC semicircles was approximately centered beneath the external lens. For the microscope experiments, samples were illuminated from below by a Redmi 3S phone (Xiaomi, Beijing, China), with a 720×1280 pixel screen and a pixel density of 294 PPI. The phone was placed approximately 2 cm below the sample, and was placed by hand such that the center-line of the DPC semicircles was approximately centered beneath the objective. Identical semicircle patterns as in the iPhone case were projected to the screen using the WPS Office application for Android (Kingsoft, Zhuhai, China).

4.3. Image analysis

In order to generate the final differential phase contrast (DPC) images, normalized image difference has to be performed. Image arithmetic was done using Fiji (ImageJ) software, as well as further image analysis.

4.4. Samples

Polystyrene beads with 3 μm diameter were purchased from Corpuscular, Inc. and diluted in distilled water (1:1000 beads to water) before use. To image the beads, 50 μL of the diluted suspension was pipetted onto a cover slip. Human epithelial cheek cell (HECC) samples were prepared for imaging by pipetting 50 μL of 0.9% NaCl solution onto a cover slip, placing the cells into the water drop, then adding another cover slip on top. The HECC were originally collected by taking a tooth pick and swabbing the inside of the cheek. Mouse monocyte macrophage cells (J774A.1 cells) were generously gifted by Prof. Adam Hendricks' laboratory at McGill University. Mouse neuroblastoma cells (N2a cells), and mouse embryonic carcinoma cells (P19 cells) were generously gifted by Prof. Allen Ehrlicher's laboratory at McGill University. Mouse bone marrow-derived macrophages were generously gifted by Prof. Thomas Huser's laboratory at Bielefeld University. To prepare these cells for imaging, a few microliters of cells in suspension were pipetted onto a cover slip placed in a petri dish, such that the cell suspension fully covers the bottom of the petri dish and the cover slip. The petri dish was then placed in an incubator overnight to allow for cell adhesion onto the cover slip. To induce cell death (pyroptosis) in the macrophage cells, the cells were treated with 10 μM Nigericin in PBS/HEPES buffer for 0.5 to 1 hour. The blood smear images were obtained from a commercially purchased slide used for teaching purposes.

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Disclosures

The authors declare that there are no conflicts of interest related to this article.

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